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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/838,718	04/19/2001	Lothar Steidler	4779US	3041

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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	10

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/838,718	STEIDLER ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-18 is/are pending in the application.

4a) Of the above claim(s) 5 and 13 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-4,6-12 and 14-18 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 19 April 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Final Rejection

Claims 1-4, 6-12, 14-18 are pending examination.

Applicants' traversal, amendment to claims 1-3, 6, 8-11, 14, 16-18, cancellation of claims 19-20, withdrawal of claims 5, 13 in paper no. 8 is acknowledged and considered.

Foreign priority document, EPO 98203529.7, is acknowledged.

This application contains claims 5 and 13 that are drawn to non-elected invention. A complete reply to the final rejection must include cancellation of withdrawn claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because of the word "such". Correction is required. See MPEP § 608.01(b).

Claim Objections

Claim 6 is objected to because of the following informalities: Claim 6 is missing the term "disease" at the end of the sentence. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-12, and 14-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims of the instant application embrace a method of treating inflammatory bowel disease (IBD) a mammal by methods of ex vivo gene therapy by administering a composition to the mammal consisting of a bacterium that expresses a recombinant gene, encoding a therapeutic protein, wherein the bacterium is a non-invasive gram-positive bacteria.

Furthermore, and with respect to claims directed to any vector (e.g. recombinant bacterium) useful for gene therapy and directed to any treatment of a mammal; the state of the art in 1998, exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Thus, gene therapy was considered unpredictable at the time the application was filed.

Specifically, the specification contemplates a cytokine-producing Gram-positive bacterial strain can be used for the preparation of a medicament to treat inflammatory bowel disease. More specifically, the specification specifically teaches a recombinant Lactococcus lactis (L. lactis) comprising a gene encoding an IL-10 protein. The recombinant bacteria are then injected into the peritoneum of healthy mice or mice with induced colitis. The pathology of chronic colitis is characterized by a decrease in colon length and epithelial damage and infiltration of lymphocytes. Example 2, mice are euthanized and a histological score of the colon demonstrates an increase in colon length of the mice with induced colitis after the treatment with the recombinant IL producing L. lactis compared to mice with induced colitis and untreated and control mice. The specification also demonstrates the prevention of colitis in IL10-/-mice by intra-gastric inoculation with IL-10 producing L. lactis (Example 5, pages 17-18 and Figure 10).

Furthermore, with respect to claims 1-4, 6-12, and 14-18, which embrace treating a inflammatory bowel disease (IBD), the specification and the state of the art only provide sufficient guidance for how to reduce inflammation caused by colitis in mammal deficient for IL10. However, the as-filed specification does not teach nor provide sufficient guidance and/or evidence for making and/or using the claimed invention embracing **one or more reduction of inflammation by at least 50% and prevention of onset of said inflammation** in any subject. The state of the art teaches that the etiology remains poorly understood and several genetic and environmental factors have been implicated in the pathogenesis of IBD (Papadakis et al. Annu. Rev. Med., Vol. 51, pp.289-298, 2000). The state of the art further teaches IBD can be separated into ulcerative colitis (UC) and Crohn's Disease (CD) and that some animal models have some features of CD and UC, although no model has actually mirrors the changes as seen in humans

(Leach et al., Toxicologic Pathology, Vol. 27, page 125, 1999). Furthermore with respect to the animal model (IL10 deficient mice) used in the examples set forth in the disclosure, the state of the art as exemplified by Leach teaches that the role of genetic influences on colitis can potentially be evaluated in IL10 -/- mice (page 127). Leach also teaches that when administering exogenous IL10 was initiated after disease was established at 3 months of age, colitis was ameliorated but not prevented (page 128). It appears from the art of record that IL10 is one factor involved in IBD and in view of the complex nature of IBD, it is not apparent to one skilled in the art how reducing inflammation in IL10 -/- mice reasonably correlates to the method embrace in the claims.

Furthermore, with respect to the claimed invention encompassing reducing inflammation by at least 50% and prevention of onset of inflammation and in view of the unpredictability for treating or preventing IBD set forth by the art of record, it is not apparent to one skilled in the art how **reduction of inflammation and prevention of onset of inflammation** can simultaneously be in the same mammal because either the mammal has inflammation or does not have inflammation resulting from IBD. Furthermore, in view of the phrase "one or more of reduction of inflammation", one skilled in the art would understand that a subject could have several distinct types of inflammation. For example, arthritis in the hand would result in inflammation of the joint that connects the hand to the wrist. Another example is the onset of allergies, which results in the inflammation of the nasal pathways in a subject and furthermore, asthma results in the inflammation of the lungs of subject. The disclosure only provides sufficient guidance for one skilled in the art to use a recombinant IL10 producing Lactococcus for the reduction of inflammation of colitis in a mammal deficient for IL10. Therefore, since only the clinical sign

known as colitis has been well characterized and the etiology of treating IBD is not fully understood, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from reducing inflammation caused by colitis in a mammal deficient for IL10 to the claimed invention embracing **one or more reduction of inflammation by at least 50% and prevention of onset of said inflammation** in a subject susceptible or having an inflammatory bowel disease.

In addition, it is not apparent as to how one skilled in the art would be enabled to reasonably extrapolate, without undue experimentation, from reducing the inflammation caused by colitis in a **IL 10-/- mouse** to the claimed invention that would generate a treatment of IBD in a **subject** (*e.g.* bird, fish, snake, etc.) because the state of the art does not teach a representative number of species (birds, fish, etc.) having IBD. Even if a therapeutic response using an ex vivo method of gene therapy for colitis in an experimental murine model using peritoneum injection has been shown in the specification, it is not apparent as to how it is reasonably extrapolated to the claimed invention embracing any subject (bird, fish, snake, etc.).

Even if the applicants are able to overcome the concerns listed above with respect to reasonably correlating reducing inflammation caused by colitis in an IL 10-/-mouse to the claimed invention embracing **one or more reduction of inflammation by at least 50% and prevention of onset of said inflammation** in a subject against inflammatory bowel disease. There are concerns under 112 enablement for making and/or using a genus of non-invasive bacteria and/or route of delivering recombinant bacteria to a subject and/or using a genus of cytokines to treat IBD. These concerns follow:

In addition with respect to the claimed invention, the claims broadly encompass the use of any species of non-invasive genetically modified cytokine producing Gram-positive bacterial strain. The specification and the state of the art provide sufficient guidance for one skilled in the art to genetically modify either Bacillus subtilis or Lactococcus lactis; however, the disclosure does not provide sufficient guidance on manipulating any other species of bacteria including Bacillus subtilis to achieve successful expression of a cytokine (e.g. Il-10). It is well known in the art of recombinant DNA technology, that there are no methods available to successfully transform all species of Gram positive bacteria and that several types of Gram positive bacteria do not possess the qualities necessary to achieve such transformation. The claimed invention encompass a genus of non-invasive gram positive bacteria that the specification and prior art only provide sufficient guidance for one skilled in the art to make and/or use the Lactococcus lactis. However, in view of the breadth of the claims, the disclosure and the state of the art do not provide sufficient guidance for one skilled in the art to make and/or use a representative number of non-invasive Gram-positive bacteria because the use of a genus of non-invasive Gram-positive bacteria in a method of ex vivo gene therapy would require knowledge about control expression (replication of origin) in vivo of a representative number of Gram-positive bacteria before it could be used for the claimed method. Therefore, it would require one skilled in the art an undue amount of experimentation to develop techniques to transform a representative number of bacteria species.

In addition, in view of the breadth of the claims, the claimed invention encompasses that any cytokine can be used in a method of treating IBD. The state of the art and the specification provide sufficient guidance for one skilled in the art to make and/or use a nucleic acid encoding

the Il-10 protein in a method of reducing inflammation in a IL10-/- mammal, however, the specification lacks sufficient guidance for one skilled in the art to make and/or use any other cytokine in the claimed method embracing treating IBD. The state of the art provides numerous cytokines (See Kuby, Immunology, pages 304-306, 1994) and their properties (pro-inflammatory or anti-inflammatory), however, the specification lacks sufficient guidance for one skilled in the art to use any cytokine other than IL-10 (anti-inflammatory) in an ex vivo method of gene therapy for reducing inflammation in the intestine of an IL10-/- mammal. Thus, it would take one skilled in the art an undue amount of experimentation to reasonably correlate the results observed with using Il-10 to any other cytokine, let alone claims embracing any prevention of an onset of inflammation.

With respect to therapeutic methods (preventing or ex vivo gene therapy) encompassing routes of administration, the state of the art exemplified by Verma is further supported by Page et al. (DDT, Vol. 6, 2001, pp. 92-101). Page teaches that the large hurdles that need to be overcome for oral gene delivery are acid pH in the stomach, the nucleases, lipases and peptidases present in the GI tract and the poor permeability of gene vectors across the intestinal epithelium (page 92). More specifically, it is unclear from the disclosure that recombinant bacteria administered through any route other than the peritoneum route would be able to be expressed at a therapeutic level. For example, it is unclear how to avoid digestion of the bacterium, and the proteins they produce, when administered orally, or if bacteria delivered to the bronchia will produce proteins that will be absorbed and translocated to the appropriate tissue to achieve a therapeutic effect. Therefore an undue amount of experimentation would be required for one

skilled in the art to determine what routes of administration other than the peritoneum route can be used to observed an in vivo therapeutic effect.

Thus, it is not apparent as how one skilled in the art reasonably extrapolates, without undue experimentation, from the working examples to the claimed invention that would generate **one or more reduction of inflammation by at least 50% and prevention of onset of said inflammation** in any subject against any inflammatory bowel disease. Even if a protective response has been shown in IL10-/- mice, it is not apparent as to how the mouse model is reasonably extrapolated to the claimed invention, encompassing any subject particularly given that there is no evidence showing that the mice model is a general phenomenon, and given the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made do not provide sufficient guidance and/or evidence to reasonable enable the claimed invention. One would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the application's disclosure, the unpredictability of gene therapy (Anderson, *Nature*, Vol. 392, pp.25-30, 1998) and developing effective therapies encompassing administering a non-invasive cytokine producing bacteria **one or more reduction of inflammation by at least 50% and prevention of onset of said inflammation**. In addition, the presence of a working example as provided in the as-filed specification do not reasonably extrapolate to the claimed invention, particularly given that there is no evidence that the mice model is a general phenomenon for administering medicament comprising a cytokine non-invasive bacterium to a subject wherein the administration of said

medicament results in one or more reduction of inflammation by at least 50% and prevention of onset of said inflammation.

Applicants traverse the rejection under 112 enablement for the following reasons: The present invention is not related to ex vivo gene therapy, but rather recombinant bacterium. Specifically it is admitted that Anderson and Verma references are not relevant to that which is recited in claims herein; The present invention is not related to DNA vaccination, therefore McCluskie is not relevant to the claims of the present application; Applicants submit that the state of the art does provide sufficient guidance for one skilled in the art to make and/use a representative number of non-invasive Gram-positive bacteria, such as this listed above, in the method of the present invention; The present invention teaches a method of introducing any cytokine into the gut; The specification provides ample guidance to a person skilled in the art regarding how to treat a subject with inflammatory bowel disease by administering a suitable Gram-positive bacterium; Furthermore, the mouse model disclosed by the present invention is a generally recognized model for treatment of inflammatory bowel disease in any subject (See Science, 2000, 1352-1355, appendix D). See pages 7-9.

Applicants' traversal is acknowledged and is not found persuasive. Furthermore, with respect to the claimed invention, the applicants' traversal is acknowledged and is not found persuasive because the as-filed specification and/or the applicants' traversal do not provide sufficient guidance and/or factual evidence for one skilled in the art to make and/or use a representative number of non-invasive Gram-positive bacteria and what cytokines other than IL-10 can be used to treat IBD in a mammal and what routes of administration other than injection into the peritoneum are enabled to produce a therapeutic effect in a mammal having an IBD, let

alone prevent IBD. In addition, the as-filed specification and the applicants' fail to provide sufficient guidance for one skilled in the art to administer a medicament that would result in one or more of reduction of inflammation by at least 50% and prevention of onset of said inflammation.

First, with respect to the articles not displaying the state of the art for the claimed invention, the concerns set forth by Anderson and Verma are applicable to the claimed invention because the invention encompasses delivering DNA in a recombinant bacterium to a mammal. Anderson and Verma discuss the state of the art with delivering DNA using a vector (viral vector, recombinant bacterium, naked DNA, plasmid, autologous cells, etc.). While ex vivo gene therapy does encompass extracting cells from the subject to be treated and genetically modifying the cells and re-implanting the genetically modified cells back into the subject, ex vivo gene therapy encompasses on a broader skill the concerns with any type of gene therapy comprising: 1) The type of vector and amount of DNA constructs to be administered, 2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site; 3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and 4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method, See Anderson. Since the claimed invention comprises delivering a vector (recombinant bacterium) to a mammal, the concerns set forth by Anderson and Verma are applicable to the claimed invention.

In addition, with respect to the applicants' assertion that the specification provides sufficient guidance for one skilled in the art to make and/or use a representative number of non-

invasive Gram-positive bacteria, the traversal is not found persuasive because the applicants' traversal and/or the as-filed specification fail to provide sufficient guidance and/or evidence for a representative number of non-invasive Gram-positive bacterial strains. The art of record and the as-filed specification provide sufficient guidance for one skilled in the art to make and/or use the Lactococcus species. In view of the state of the art, the claimed invention is not enabled for the genus of non-invasive Gram-positive bacteria because there are a numerous number of non-invasive Gram positive bacteria known to one skilled, however, one skilled in the art would understand that each species of bacteria has a different replication of origin that is required for replication of any DNA in its genome. Without the knowledge of the replication of origins for a sufficient number of species of bacteria, it would take one skilled in the art an undue amount of experimentation to make and/or use a representative number of non-invasive Gram-positive bacteria contemplated by the claimed invention. Furthermore, the as-filed specification fails to provide sufficient guidance and/or factual evidence for one skilled in the art to reasonably extrapolate from the replication of origin of the Lactococcus species to other replication of origins in a sufficient number of other bacteria.

In addition, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [footnote omitted].

On this record, it is apparent that the specification and the applicants' traversal (See page 8 of traversal, which states, "the present invention is not intended to suggest using harmful bacterial strands such as the Examiner's points out") provide no more than a plan or invitation in view of the art of record exemplifying the unpredictability of using any non-invasive gram-positive bacteria for reducing inflammation and preventing onset of inflammation, for those skilled in the art to experiment with gram-positive bacteria so as to provide a medicament, which results in one or more of reduction of inflammation by at least 50% and prevention of onset of said inflammation as intended by the as-filed specification at the time the invention was made.

See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for what protocols are required for different bacteria other than Lactococcus species for treating colitis in a mammal deficient for IL10, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the assertion set forth above to the claimed invention.

In addition, with respect to the applicants' traversal that any cytokine can be used to treat IBD in a mammal, the traversal is not found persuasive because the art of record teaches that Crohn's disease (CD) and ulcerative colitis (UC) have been associated with increased pro-inflammatory cytokines such as IL-1, IL-6 (see prior PTO-892, Leach et al. 1995, page 123). In

view of the art of record, it is not apparent why one skilled in the art would want to use any cytokine other than IL-10 because several cytokines are associated with pro-inflammatory response that would hinder the treatment of IBD in a mammal rather than reduce IBD in a mammal. While it acknowledged, that the as-filed specification is not required to teach all species under a genus, the specification is required to teach which species are enabled or not-enabled (See Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997). Thus, the as-filed specification and/or the applicants' traversal fail to provide sufficient guidance for one skilled in the art to use any cytokine other than Il-10 for administering a medicament (cytokine producing bacterium) to reduce inflammation resulting from colitis in a mammal deficient in IL 10, however, this does not reasonably extrapolate to claimed invention embracing one or more of reduction of inflammation by at least 50% and prevention of onset of said inflammation.

Furthermore, with respect to applicants' traversal that the mouse model disclosed in the present invention is a generally recognized model for treatment of IBD in any subject (See Science, 2000, 1352-1355, the abstract states, "this approach **may** lead to better methods for cost-effective and long-term management of IBD in humans"). This phrase is not found persuasive because the art of record provides numerous statements displaying that that IBD is a generic term used to describe a group of idiopathic inflammatory intestinal conditions in human (Leach, Toxicologic Pathology, abstract). Also see Papadakis et al. (Annu. Rev. Med., 2000); Targan et al, (Nature Medicine, 1995); Korelitz, (Gastroenterologist, 1995). Crohn's Disease is an eponym that describes the convergence of many clinical signs and symptoms (Targan et al. Nature Medicine, Vol. 1, pp 1241, 1995). Thus, since only the clinical sign known as colitis has

been well characterized and **the etiology of treating any IBD** is not fully understood, it would take one skilled in the art an undue amount of experimentation to administer a medicament which results in one or more of reduction of inflammation by at least 50% and prevention of onset of said inflammation since the etiology of IBD is unknown. Therefore, the as-filed specification and/or the applicants' traversal only provide sufficient guidance and/or evidence for one skilled in the art to make and/or use a genetically modified L. lactis expressing Il-10 to treat colitis, however, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from treating the clinical sign colitis to administer a medicament which results in one or more of reduction of inflammation by at least 50% and prevention of onset of said inflammation encompassing numerous clinical signs or symptoms in a subject.

In addition, the applicants' traversal does not provide sufficient guidance and/or factual evidence to overcome the concerns set forth under 112 enablement (e.g. Page et al. DDT, 2001) for using any route of administration because the traversal does not address this issue. Therefore, the as-filed specification is only enabled for injecting into the peritoneum of a mammal deficient for Il10. However, it would take one skilled in the art an undue amount of experimentation to reasonably correlate reducing inflammation resulting from colitis to administering a medicament, which results in one or more of reduction of inflammation by at least 50% and prevention of onset of said inflammation in a subject that might have IBD.

In addition, the applicants' traversal does not provide sufficient guidance and/or factual evidence to overcome the concerns set forth under 112 enablement for how one skilled in the art reasonably extrapolates, without undue experimentation, from reducing inflammation resulting from colitis in a mammal to the claimed invention that would generate one or more of reduction

of inflammation by at least 50% and prevention of onset of said inflammation in a subjects (*e.g.* birds, fish, mammals, etc.). Even if a therapeutic response using an ex vivo method of gene therapy for colitis in an experimental murine model deficient in IL10 using peritoneum injection has been shown in the specification, it is not apparent as to how it is reasonably extrapolated to the claimed invention, encompassing administering a medicament, which results in one or more of reduction of inflammation by at least 50% and prevention of onset of said inflammation in a subject.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-4, 6-12, and 14-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "**one or more reduction of inflammation by at least 50% and prevention of onset of said inflammation**" in claims 1-4, 6-12, and 14-18 is a relative term, which renders the claim indefinite. The phrase "**one or more reduction of inflammation by at least 50% and prevention of onset of said inflammation**" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The claims do not define the metes and bounds of the phrase because it is not apparent what the claims are particularly pointing out and distinctly claiming. It is not apparent how administration of a medicament results in simultaneously reducing inflammation by at least 50% in a mammal and prevention of onset of inflammation in the same mammal because how can prevention occur if the mammal

already has inflammation. Furthermore, the metes and bounds of the phrase "one or more of reduction of inflammation" are not defined by the claims because it is not apparent what inflammation in a mammal is being reduced. If the inflammation is caused by IBD, it is not apparent how the medicament can result in the reduction in one or more inflammation since only one site of inflammation of would be observed in the mammal (e.g. intestine).

Claims 1-4, 6-12, and 14-18 are vague and indefinite as to what is intended to be encompassed with regard to the phrase "**reduction of inflammation**". While a subject would have inflammation in the subject's intestine resulting from IBD, the claims do not define and particularly point out what type of inflammation is being reduced. In the art of reducing inflammation in a subject, inflammation in a subject can encompasses completely distinct areas of the subject's body. For example, arthritis in the hand would result in inflammation of the joint that connects the hand to the wrist. Another example is the onset of allergies, which results in the inflammation of the nasal pathways in a subject and furthermore, asthma results in the inflammation of the lungs of subject. Thus, it is unclear what relationship between reduction of inflammation and IBD is intended to be encompassing by the recitation of the phrase "**reduction of inflammation**".

Claims 1-4, 6-12, and 14-18 recite the limitation "said inflammation" on page 3. There is insufficient antecedent basis for this limitation in the claim. The term "said inflammation" lacks antecedent basis because of the reasons set forth in the prior 112 second rejection because the claim does not define which type of inflammation is being reduced in the subject. In addition, it is not apparent if the term is referring to IBD or inflammation.

Claim Rejections - 35 USC § 102

Applicants' traversal is acknowledged and the rejection under 102(b) for claims 1-4, 6, 10-12, and 14-18 is moot because of the amendment to the independent claim, which now reads on a method of treating IBD in a subject, said method comprising: administering a medicament comprising an amount of a cytokine-producing non-invasive Gram-positive bacterial strain to said subject, wherein the administration of said medicament results in **one or more reduction of inflammation by at least 50% and prevention of onset of said inflammation**. The amendment now specifically claims a method of reducing inflammation and preventing the onset of inflammation in a subject and no longer reflects on the prior art.

Claim Rejections - 35 USC § 103

Applicants' traversal is acknowledged and the rejection under 103(a) for claims 1, 2, 7-9, and 15-17 is moot because of the amendment to the independent claim (claim 1) and for the same reasons set forth under the 102.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

Brian Whiteman
Patent Examiner, Group 1635
7/14/02